Remarks:

Claims 3-4, 8-12, 15-19, 21-25 and 31 remain for consideration in this application with claims 12, 19, and 31 being in independent format. Claims 12, 15-19, 22-25, and 31 have been amended.

As an initial matter, Applicant wishes to thank Examiner Horning and Primary Examiner Mary Mosher for their time and consideration during an interview conducted on September 6, 2007, and apologizes for not including the interview summary in the previous response. Briefly, Applicant's representatives met with the Examiners and discussed using the phrase "determining the probability of" instead of the term "predicting" in the claims. In accordance with this discussion, claims 12, 19, and 31 have been amended to more precisely define the method recited in the claims. Specifically, Applicant has replaced the term "predicting" with the phrase "determining the probability of" in order to avoid further confusion as to Applicant's intended understanding of the claims. Specific support for this amendment can be found in the specification on page 3, lines 11-12, 15-17; and page 4, lines 23-25, 29-31. Applicant's representatives also discussed the differences between acute and chronic HCV infection with the Examiners. The Examiner suggested that any ambiguity between these two stages in the infection could be avoided if Applicant framed the claimed method in terms of determining the probability that an individual has developed chronic HCV or has cleared the HCV infection. In accordance with this suggestion, Applicant has amended claims 12, 19, and 31 to recite this distinction. Finally, Table 1 and a possible discrepancy between the recited OD readings in claims 15-18 and 22-25 were also discussed. Applicant's representatives have conferred with the inventor named in the present application and have amended claims 15-18 and 22-25 to clarify that the measured OD of the sample is at 450 nm, while the negative control is the reference OD reading that is taken at 660nm to ensure validity of the measurements.

Turning now to the Office Action, Applicant notes with appreciation that the previous rejections based upon of 35 U.S.C. § 112, first paragraph, for lack of enablement and written description have been withdrawn.

However, the Examiner has rejected the claims as being obvious over the combination of Fong et al. (hereinafter "Fong") and Fabrizi et al. (hereinafter "Fabrizi). In particular, the Examiner argues that Fong discloses the clinical significance of HCV RNA status and its correlation to antibodies to structural HCV antigens. The Examiner acknowledges that Fong does not disclose the use of measuring optical density values. However, the Examiner asserts that Fabrizi teaches a statistically significant difference between HCV RNA positive and negative patients concerning the presence of anti-HCV IgM antibodies. The Examiner also asserts that Fabrizi discloses a significant relationship between optical density values and anti-HCV IgM, NS3, NS5, and core reactivity. Thus, the Examiner concludes that "[i]t would have been obvious to one of ordinary skill in the art to combine the teachings of Fong et al. and Fabrizi et al. in order to measure the optical densities of samples in ascertaining the prevalence of HCV RNA in the serum, [which in turn,] would allow one to predict whether a patient has cleared HCV or has chronic HCV." Office Action, 12/06/07, page 5.

Applicant respectfully submits that independent claims 12, 19, and 31 are not obvious in view of Fabrizi and Fong for at least the following reasons. In particular, no combination of these reference teaches or suggests each and every limitation recited in the claimed methods, and one having ordinary skill in the art would have had no "apparent reason" to combine and/or modify these reference to arrive at the claimed methods. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. ___, ___, 82 U.S.P.Q.2d 1385, 1396 (2007). In addition, even if one of ordinary skill in the art was motivated to make this modify and/or combine Fabrizi and Fong, there would not have been a reasonable expectation of success in doing so, as explained in more detail below. *PharmaStem Therapeutics,*

Inc. v. Viacell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007) (decided after *KSR, citing Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006)).

The present invention provides a method for determining the probability of whether an individual has chronic HCV infection or has cleared the infection using antibody-based assays. The Examiner's attention is directed to the attached Declaration, executed on May 12, 2008 by Mark E. Magee. Mr. Magee is the Vice President of Laboratory Operations at Clinical Reference Laboratory, Inc., the assignee of the present application. As shown in paragraph 1, at the time of the present invention, Mr. Magee would have been considered a person skilled in the art of clinical laboratory testing. In paragraph 4 of the Declaration, Mr. Magee explains that at the time of the present invention, positive results from an antibody-based assay were used primarily to document HCV exposure, but could not distinguish between infectious individuals (i.e., chronic) and non-infectious individuals (i.e., cleared). Thus, PCR techniques had to be performed to determine whether viral particles were still present, indicating a chronic infection. At the time of the present invention, the cost to confirm a single case of HCV infection using PCR was around $120 per test. Even today, PCR testing is still cost prohibitive, at about $100 per test, especially when testing a large number of samples/individuals. By comparison, the cost of an antibody-based assay is about $10-12 per test.

In practice, the claimed methods provide the advantage of permitting one of ordinary skill in the art to positively identify individuals with a very low probability of having a chronic infection who *do not* need to be further tested for HCV RNA. The claimed methods also to permit one of ordinary skill in the art positively identify individuals with a high probability of having a chronic infection who *do* need further testing. Thus, unlike the prior art methods, depending upon which group is the focus of the testing, the present methods can be adapted so that one having ordinary skill in the art can identify individuals who have a very high probability of *not* being chronically infected or individuals with a very high probability of being infected, or both.

In contrast, as Mr. Magee attests, neither Fong, nor Fabrizi teaches or suggests that an antibody-based assay can be used to qualitatively determine the probability that an individual is chronically infected or has cleared the infection, as in the present methods. In addition, neither reference provides specific OD readings which are correlated with certain probabilities of chronic or cleared infection as in claims 15-18, 22-25, and 31. Thus, as explained in more detail below, the claimed methods would not have been obvious to a person of ordinary skill in the art in view of these references, and the rejection should be withdrawn.

According to Mr. Magee, Fabrizi only *purports* to disclose a correlation between the prevalence of anti-HCV IgM antibodies and the presence of HCV RNA in serum that would permit a determination of the probability that the individual has chronic HCV, as the Examiner argues. A closer inspection of the data in Fabrizi reveals to a person skilled in the art that Fabrizi focuses only on a one-way correlation, and fails to examine or discuss the entirety of the data from the study, emphasizing only the seemingly favorable statistics. In particular, one having ordinary skill in the art would recognize that the antibody tests in Fabrizi had terrible sensitivity and poor negative predictive value, which, in fact, would not permit one of ordinary skill in the art to determine the probability that an individual has chronic HCV infection or has cleared the infection, as claimed.

The Examiner's attention is directed to Table 1 on page 5 of the Declaration, where the data from Fabrizi has been reproduced to aid in understanding the true significance this data would have to one of ordinary skill in the art. A total of 78 end-stage renal disease patients were tested in Fabrizi. Of those patients, 17 tested positive for HCV antibodies, while 61 tested negative for HCV antibodies in the antibody-based assays. As Mr. Magee explains, testing positive for anti-HCV IgM in Fabrizi strongly suggests the presence of HCV RNA in serum, because of the 17 patients who tested positive for anti-HCV, 15 subsequently tested positive for HCV RNA using PCR (i.e., the true

positives). Thus, the antibody tests in Fabrizi only resulted in 2 false positives, giving the test good positive predictive value. However, of the 61 patients who tested *negative* for anti-HCV IgM, ***30 actually tested positive for HCV RNA*** in serum using PCR. Thus, the antibody-based assays in Fabrizi resulted in ***30 false negatives*** (i.e., individuals who were chronically infected, but who went undetected by the assays).

As Mr. Magee points out, and as would have been recognized by one skilled in the art, **67% of the chronically infected patients were not identified by the antibody tests** in Fabrizi, giving the assay a *very poor* negative predictive value. Therefore, although testing positive for anti-HCV IgM in Fabrizi was a strong indicator of chronic infection, testing negative for anti-HCV IgM could not be used to indicate or predict that the individual has cleared the infection. On the contrary, as shown from the data above, there was still a very strong likelihood that the individual was chronically infected, despite testing negative for anti-HCV IgM. One skilled in the art would recognize that *all* of the individuals in Fabrizi would still need to be tested using expensive PCR to confirm chronic HCV status, since testing negative for anti-HCV IgM does not eliminate that individual from the testing pool, because there is still a high probability that they are chronically infected. Thus, the teachings of Fabrizi would not permit one of ordinary skill in the art to differentiate between individuals having chronic infection and those who have cleared the infection using antibody-based assays.

Moreover, Mr. Magee explains that the information disclosed by Fabrizi would not have been helpful to one of ordinary skill in the art and would not have motivated one of ordinary skill in the art to even try antibody-based assays. That is, the lack of sensitivity and poor negative predictive value demonstrated by these types of assays, according to Fabrizi's data, would simply not be tolerated in a practical setting. Rather, to be useful, the assay must allow a clinician to identify *true negatives*, i.e., those individuals who *do not* need to undergo further testing using

expensive PCR. As Mr. Magee attests, the assays of Fabrizi only allow one skilled in the art to identify those individuals who *do* need to undergo testing (those with a high probability of being chronically infected). However, every member of the test groups still needs to be tested using expensive PCR because the assays in Fabrizi do not weed out the true negatives. As explained above, just because an individual tests negative for anti-HCV in Fabrizi does not mean they are not chronically infected. Thus, as a practical matter, the correlation disclosed by Fabrizi is not helpful, and does not provide the advantage of being able to eliminate non-infectious individuals during the first round of testing using the inexpensive antibody-based assays. In addition, Fabrizi does not provide any actual OD readings and does not correlate the test results with certain probabilities that an individual is chronically infected or has cleared the infection, as in claims 15-18, 22-25, and 31.

Simply put, to one of ordinary skill in the art, Fabrizi does not provide any meaningful disclosure that would lead one skilled in the art to use an antibody-based assay to distinguish between chronically infected and non-infectious individuals, as in the claimed methods. In addition, Mr. Magee explains that one skilled in the art would view the data of Fabrizi to be limited to patients with end-stage renal disease (ESRD). That is, the parameters for the sample set in Fabrizi were limited to ESRD patients who also tested positive for antibodies of the IgM class in serum. Indeed, Fabrizi acknowledges the limited applicability of the data, stating that "[t]he significance of anti-HCV IgM antibody in different high-risk patient groups [besides ESRD] is uncertain; there are some reports with conflicting results at this time." Fabrizi et al. page 317. Fabrizi goes on to cite a handful of conflicting reports regarding the significance of IgM antibody in individuals with HCV, while noting that its significance in other diseases like hepatitis B is more clear. In view of the conclusions drawn by Fabrizi, it is unlikely that one skilled in the art would use the data from Fabrizi in a broader application, such as for general population modeling for determining the

probability of HCV infection status. Accordingly, Applicant respectfully submits that independent claims 12, 19, and 31 are patentable over Fabrizi and the rejection should be withdrawn.

Moreover, the teachings of Fong cannot cure the deficiencies of Fabrizi with regard to the claimed method. In particular, as Mr. Magee explains in paragraph 9 of the declaration, although the assays in Fong detect antibodies reactive with several antigens, as argued in the Office Action, the samples in Fong are *not* contacted with a plurality of different antigens reactive with different antibodies in a single assay or solution, as in the claimed methods. Rather, the samples in Fong were tested using "*individual* antigen ELISAs" in which each individual antigen was "separately coated on to [*sic*] microwells." Fong et al., page 254. The titers of antibodies reactive with the *individual* antigens were then observed and recorded. Thus, unlike the presently claimed methods, Fong did not actually run assays using multiple antigens in a single assay or solution, as the Examiner asserts.

Applicant respectfully submits that there is nothing in Fong that would teach or suggest using a plurality of different antigens in a single assay or solution. Rather, Mr. Magee attests that Fong actually teaches away from this. In particular, the only statistically significant correlation of antibodies to HCV infection status disclosed in Fong pertained to the anti-E2 titers. The remaining disclosed antigens c22-3, c200, c33c, and c100-3 from the ELISA, and c100-3, c22c, c22-3, and 5-1-1 from the RIBA 2.0 were reported as being inconclusive. As Mr. Magee explains in paragraph 9 of the declaration, one having ordinary skill in the art based upon the teachings of Fong would have been discouraged from including any of these other antigens in the assay, because the other antigens would have been expected to only obscure the test results. That is, one skilled in the art would have expected only E2 yield to legitimate results, and would not have been motivated to use a plurality of antigens in the assay, as in the claimed methods.

In addition, Mr. Magee further explains that even if one skilled in the art was motivated to use a multi-antigen assay, that person would not have used any of the antigens disclosed in Fong,

besides E2. In particular, Fong teaches that antigens c22-3, c200, c33c, c100-3, and 5-1-1 do not correlate to the presence of HCV RNA in serum. Thus, one skilled in the art would have had to determine through experimentation which other antigens could be included in the assay to give a correlation to the presence of HCV RNA in serum. As Mr. Magee attests, Fong provides no guidance for one skilled in the art to select any additional antigens beyond those antigens individually tested from the disclosed assays.

According to Mr. Magee, determining which antigens to include in a multi-antigen assay would require each sample to be assayed with an individual antigen and an antibody-based assay. These results would then have to be confirmed using expensive and time-consuming PCR. The results would then have been compared, computed, and analyzed to determine which antigens provide a statistically significant correlation to the presence of HCV RNA in serum. In addition, in order to broadly conclude that a given antigen provided a correlation to the presence of HCV RNA in serum, the tests would have to be performed on a sufficiently large and representative sample set. As Mr. Magee attests, at the time of the present invention, this would have been considered undue experimentation. That is, in view of the costs associated with the assays and PCR tests, the equipment required to run these tests, the number of samples involved, and the lack of guidance in the prior art, it would have required much more than routine experimentation to arrive at a multi-antigen assay. In addition, as can be seen from Fong itself, choosing suitable antigens involves a high degree of unpredictability, which only further increases the undue nature of the experimentation involved. Moreover, Fong specifically recognizes that "attempts to identify specific serologic markers which correlate with disease status in HCV infected patients have been largely unsuccessful." Fong et al., page 256. Whereas, the *only* antibodies in Fong shown to have a statistically significant correlation were E2 antibodies. Thus, one of ordinary skill in the art would

not have had a reasonable expectation of success in finding alternate antigens to modify the assay of Fong to include a plurality of antigens.

In addition, as noted on page 257 of Fong, E2 is a hypervariable sequence within the HCV genome, prone to rapid and spontaneous mutation. Thus, Mr. Magee explains that the fact that anti-E2 titers happened to be lower in nonviremic patients in Fong's study, does not necessarily permit this correlation to be applied to all HCV antigens or HCV infected individuals. Rather, in view of the hypervariability of the E2 sequence, one skilled in the art would consider using E2 as a regular marker for HCV infection status to be unreliable and prone to false negatives. It would also require commercially-available assays to be constantly updated to keep up with the mutated sequences. As a practical matter, especially in a clinical setting, one skilled in the art would not use E2 antigens in an assay to determine the probability of whether an individual is chronically infected or has cleared the infection.[1] Thus, like Fabrizi, the correlation provided by Fong is not helpful and does not provide any meaningful disclosure that would permit one skilled in the art to deduce or derive the claimed methods. Thus, Applicant respectfully submits that independent claims 12, 19, and 31 are patentable over Fong and the rejection should be withdrawn. In addition, although Fong makes the correlation between anti-E2 titers and HCV infection status, Mr. Magee points out that Fong does not provide any actual OD readings and does not correlate the test results with certain probabilities for being chronically infected or having cleared the infection, as in claims 15-18, 22-25, and 31.

Finally, Mr. Magee notes that, like Fabrizi, the data from Fong has limited applicability because of the strict criteria for patient eligibility and small size of the sample set (13 patients total). That is, Fong was limited to adult patients with confirmed anti-HCV reactivity and persistently

[1] Indeed, as Mr. Magee explains, the working examples in the present application describe two commercially available assays, neither of which uses E2 antigens or proteins encompassing the E2 antigen. Rather, the Abbott HCV EIA 2.0 assay contains c100-3, HC-31, and HC-34 antigens, and the ELISA ORTHO HCV 3.0 contains c22-3, c200, and NS5 antigens. As noted above, Fong actually teaches away from many of these antigens.

normal liver tests for 6 months. The patients were limited in their alcohol consumption and history of consumption, and those testing positive for hepatitis B surface antigen (HBsAg) or anti-HIV in serum were excluded. Thus, one skilled in the art would recognize that any certain probabilities or correlations deduced or derived from Fong would not be applicable to the general population. As Mr. Magee explains, for data to be useful in a broader application, the sample set from which the data will be collected needs to embrace all sources of variation that are embraced by the target population, i.e., the group to which the results from this data will ultimately be applied.

In the present application the working example tested 1,200 serum samples, where the only criteria was that the sample had an ALT concentration of above 41 U/ml. In contrast, Fabrizi and Fong are each concerned with a very specific set of patients with defined symptoms or conditions. Mr. Magee attests that these patients are not representative of the general population, or even of the population of individuals testing positive for anti-HCV antibodies. Thus, according to Mr. Magee, one of ordinary skill in the art would recognize that attempting to extrapolate from these defined samples sets would not yield accurate or predictable results when the correlations are applied to a larger population.

More importantly, in view of the defined patient groups disclosed in each reference, one having ordinary skill in the art would simply not be motivated to combine the teachings of Fabrizi and Fong. That is, there would be no technical or scientific motivation to combine the data for individuals with ESRD who also test positive for IgG (Fabrizi), with data for individuals testing positive for anti-HCV, who also have persistently normal liver tests for 6 months, do not consume more than 80 grams of alcohol/day, and do not have chronic liver disease, or HBsAg or anti-HIV in serum (Fong). Rather, Mr. Magee attests that one skilled in the art would not be motivated to make this combination.

In view of what Fabrizi and Fong would have taught to one of ordinary skill in the art, as evidenced by the attached Declaration, it cannot be said that either reference, either alone, or in combination "would allow one to predict whether a patient has cleared HCV or has chronic HCV," as the Examiner asserts in the Office Action. Page 5. In particular, no combination of these references teaches a method of determining the probability that an individual has chronic HCV infection or has cleared the infection using an assay with a plurality of antigens in a single assay or solution, as recited in independent claims 12, 19, and 31. In addition, neither reference provides helpful or meaningful data that would permit one skilled in the art to distinguish HCV infection status from the disclosed data, as claimed, either directly, or by extrapolating the trends disclosed in each reference. Finally, neither reference teaches or suggests any actual OD readings and neither reference correlates the test results with certain probabilities for being chronically infected or having cleared the infection, as recited in claims 15-18, 22-25, and 31. For at least the foregoing reasons, Applicant respectfully submits that independent claims 12, 19, and 31 are patentable over Fabrizi and Fong, and respectfully requests that the rejection be withdrawn. In addition, while dependent claims 3-4, 8-11, 15-18, and 21-25 recite additional patentable features, these claims should also be patentable as depending from patentable independent claims.

In view of the foregoing, a Notice of Allowance appears to be in order and such is courteously solicited. If any questions should remain, the Examiner is encouraged to contact the undersigned.

Any additional fee which is due in connection with this amendment should be applied against our Deposit Account No. 19-0522.

Respectfully submitted,

Date: May 23, 2008 By /John Michael Collins/

John M. Collins, Reg. No. 26262
Hovey Williams LLP
10801 Mastin Blvd., Suite 1000
84 Corporate Woods
Overland Park, Kansas 66210
T 913.647.9050
F 913.647.9057

ATTORNEY(S) FOR APPLICANT(S)